Coding Drug Effects on Laboratory Tests for Health Care Information Systems

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Drugs interfere with laboratory diagnostics. This interference is not only confusing for clinicians but may lead to wrong diagnoses or treatments as well as unnecessary further tests. However, at the moment the drug-laboratory interferences are usually ignored in patient care because clinicians do not know or remember these properties of drugs. In Turku University Central Hospital we are now able to bring this information automatically available for clinicians by using a computerized system for linking individual patient medication data with laboratory information system. For this purpose, we are building a rule base containing the effects of drugs on laboratory tests. In order that the rule base would give the maximum benefit for all users, even other hospitals, the data included have to be classified and coded properly taking into account the various requirements and needs of all users. In this paper we introduce a coding scheme for classification and coding of drug effects on laboratory tests.

INTRODUCTION

A vast amount of information about drug effects on laboratory tests exists in the literature. This information can be found in several catalogues (1,2) and in some databases. There are even a few stand-alone computer programs planned for this purpose. However, the data are variegated and one has to be active and keenly interested in the topic to reach the information. Clinicians seldom have time to acquaint themselves with the data in question. The most reasonable way of bringing the data from catalogues to clinical work is to build advanced computerized systems which continually monitor the patient data and alarm the clinician when necessary. The HELP system developed in the LDS Hospital in Salt Lake City is one of the most advanced hospital information systems (3, 4). It has turned out to be very useful especially in finding adverse drug reactions (5,6) and improving empiric antibiotic selection (7). Computerized medication monitoring has also been used successfully in the field of drug interactions (8). The next step in helping clinicians in patient care is to build a rule base for drug effects on laboratory tests in order to enable alarming of these interferences.

Coding patient medication profiles in a hospital information system is somewhat problematic. Clinicians and nurses usually use trade names when dealing with drugs. On the other hand, information about drug interactions and drug effects on laboratory tests is most often listed in catalogues using generic names. The trade names and generic names can be linked very easily in computerized systems but other problems still remain. Neither generic names nor trade names reveal anything about the drug itself. For example the trade name or generic name of a drug does not necessarily reveal whether the drug belongs to penicillins. Systems have been developed in which families of drugs are defined using generic names. In some projects, such as Systematized Nomenclature for Medicine (SNOMED) and Unified Medical Language System (UMLS), medical terminology has been coded using standardized vocabulary (9). These terminologies are also used in some applications related to patient medication (7,10). These standards are, however, of limited use for coding of drug effects on laboratory tests for several reasons: 1) The rule bases would need to be translated, when transformed to another language area. 2) It is easier to code the severity of the effects with numbers or single letters than with words. 3) The spelling of drug names varies.

In our opinion, replacing names using standardized coding schemes is needed to keep database structures simple. A good example of clinically useful coding system is the ATC code for human drugs, which is widely used especially in Europe (11). The code reveals not only the specific generic substance of the drug, but also the hierarchical structure of the group the drug belongs to. For example, the code for diuretics is C03 and for furosemide C03CA01.

An advanced hospital information system is a precondition for a computerized alarming system. In Turku University Central Hospital, we have in our information system a separate ATC-coded database for the individual medications of the patients (12).

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From our laboratory database we have built a link to this medication database and to a rule base in which we intend to store the effects of drugs on laboratory tests. Consequently, the structure of the system is completed, but the data concerning drug-laboratory interferences have to be stored in a rule base. As mentioned, the amount of information is huge but the quality of the references concerning drug effects on laboratory tests is highly varying. Most of the studies are case reports, which are interesting mainly from the scientific point of view, but the clinical significance of the results yet remains questionable. Therefore, the data have to be evaluated and classified carefully before they are used in clinical decision support. In particular, the classification is essential in order to build a rule base which can also be used in other hospitals.

In our pilot study (276 patients) concerning TSH, T4 and FT4 tests, the incidence of drug-laboratory interferences was 52% (13). This means that one half of the patients had at least one drug affecting the thyroid function tests above when we included all the possible interferences reported in the literature (1). The fact that drug effects on laboratory tests occur so frequently, convinced us that an accurate description of the effects is needed to be able to give alarms on only relevant interferences. This inspired us to develop a separate coding scheme, the DLI code. This code reveals the most important features of the effect immediately and gives the clinician quite a precise idea of the interference without great efforts. In this paper we propose a coding scheme for coding drug effects on laboratory tests and show how the code works in practice by coding a group of drug effects found in catalogues.

METHODS

Factors Influencing the Classification of Drug Effects on Laboratory Tests

Our aim is to develop a code for drug effects on laboratory tests. The basis of this code is a classification which has to consider several parameters:

-nature of effect: analytical or physiological
-direction and strength of effect
-level of documentation
-sex of patient
-age of patient
-onset of effect
-duration of effect
-diseases of patient
-clinical significance of effect

The nature of a drug effect on a laboratory test can be analytical or physiological (1). If the effect is analytical (14), it refers to only one method which has to be mentioned in the rule base. A hospital using this kind of classification is then able to compare their method with the method in question and decide whether the drug-laboratory interference should be taken into account or not. Nowadays, hospitals often use same standard methods, which facilitates the situation.

If the drug effect on a laboratory test is physiological (15), it is in a way "real" and independent of the method used in measuring. But in this case the sex and age and probably the diseases of the patient have to be considered. A great deal of analytes are equally affected by drugs in males and females but for instance endocrinological measurements, especially sex hormone tests, are obvious exceptions. Age is another factor which may greatly affect the interference, again particularly in the endocrinological field.

Diseases affect several laboratory tests. In these cases it is not always evident whether the laboratory interference is caused by a drug or a disease. Even such preanalytical parameters as obesity and high blood pressure may greatly interfere with laboratory tests. In congestive heart failure low plasma sodium levels are associated with the severity of the disease and survival. However, it is not clear if the hyponatremia is associated with the disease or if it only reflects the abundant use of diuretics.

The onset of the effect is not inevitably the same as the onset of medication. The drug-laboratory interference may, for example, begin only after a week of drug intake. The duration of the laboratory interference may vary a great deal depending on the half-life of the drug. Some interferences have resolved in one week but for instance the effect of amiodarone may last for half a year (15). The duration of the effect is not a parameter which ought to be tested widely but the expert knowledge of the clinical pharmacologists is of great importance here.

The level of documentation is one of the most important factors influencing the classification. At the moment, the drug-laboratory interference data are mainly based on case reports and can not be considered well documented. To verify the effect a clinical trial is often needed. However, it is not appropriate to perform separate studies only to evaluate drug effects on laboratory tests. Instead of that, interferences can be tested within other drug studies with healthy volunteers or relevant patient population. The patient population in these studies does not have to be large. If the effect of a drug is significant it should appear in nearly every patient. There are many interferences which are well known and the actual testing of these effects would serve no purpose.

The clinical significance of the drug-laboratory interference is not a clear concept. It is by no means directly related to the incidence or statistical

significance of the effect. For example, alerting to frequent and widely known drug-laboratory interferences, such as the hyponatremic effect of diuretics, is not most important in an alarming system. At the same time, the incidence of the effect of chlorpromazine on prolactin values may be lower but the clinical significance of this interference is great.

Preparation of a Code

To develop a perfect code, all the above mentioned parameters are to be classified. As a pattern for this code, we may to some extent use the classification of drug interactions completed by Folke Sjöqvist (16). In this classification interactions are grouped on the basis of two parameters: clinical significance and nature of documentation. In both groups there are four stages.

In the preparation of a code for drug effects on laboratory tests, our starting point is the nature of effect. It could be coded as follows:

A. Physiological effect
B. Analytical effect
C. Both analytical and physiological effect
D. Unknown mechanism
E. No effect

The direction and strength of the effect has to be coded carefully. An ideal situation would be that each drug clearly decreases or increases or has no effect on a laboratory test. But in practise the effect may also be transient. It may, for instance, disappear in a couple of weeks. In some cases there is even contradictory information of the effect in the literature. We have arrived at the following coding:

1. Decreasing effect (>30 %)
2. Slightly decreasing effect (<30 %)
3. Transient decreasing effect
4. No effect
5. Transient increasing effect
6. Slightly increasing effect (<30 %)
7. Increasing effect (>30 %)
8. Contradictory data on the effect

The level of documentation of a drug-laboratory interference has to be defined carefully. The classification of this parameter requires a lot of work. All the references in the catalogues and databases concerning drug-laboratory interferences have to be evaluated and a great number of new trials has to be carried out. As a result the drug-laboratory interferences could be coded according to the pattern of drug interaction classification (16) mentioned earlier with the exception of one extra class: the assumed or widely known interferences. We propose the following levels of documentation:

A. The interference is documented in controlled clinical studies with relevant patient material
B. The interference is documented in studies with healthy volunteers
C. The interference is established in well documented case reports
D. The interference is detected in incomplete case reports or is not yet documented
E. The interference is assumed or widely known

The sex of the patient is easy to code:

1. Interference reported in males
2. Interference reported in females
3. Interference reported in males and females

Though age may affect the interference, it is usually impossible to define precise age limits for drug effects. Still, a rough classification may give further information of the effect as follows:

1. Interference reported in adults
2. Interference reported in children
3. Interference reported in adults and children

For the onset of the effect we propose the following classification:

1. The effect begins immediately
2. The effect begins in one week
3. The effect begins in one month
4. Unknown

The maximum duration of the interference after stopping drug therapy could be divided in four groups:

1. One week
2. One month
3. Six months
4. Unknown

The clinical significance of a drug-laboratory interference is difficult to define. One aspect of clinical significance is the theoretical risk of danger for the patient in case of misjudgment. Another aspect is the risk of wrong diagnosis and unnecessary further tests and expenses for the hospital. At this point the classification could be designed as follows:

A. Major risk for patient
B. Minor risk for patient or risk of wrong diagnosis
C. No risk for patient

The diseases of the patients are impossible to classify in this connection. It remains for the clinician to assess if the diseases of the patient interfere with the laboratory tests.

RESULTS

Examples of the Usage of the Proposed Code

As an example we have coded a group of drug-laboratory interferences reported in the literature (1). The code is demonstrated in Table 1.

Note that corticosteroids have different effects in children and adults. This can be coded easily, since several codes can be used for the same laboratory test and drug combination, for example, A7A3244B for children and A2E3144B for adults.

Note also that a group of drugs can be coded in a smart way using the ATC code. Here, the beginning of the code H02AB reveals that the drug is a

Table 1. Examples of coding drug-laboratory interferences. The DLI code is the Drug Laboratory Interference code proposed in this paper. On the right hand column, the information is presented as it exists in the catalogue by Young (1)

Lab Test	ATC code	Drug name	DLI code	Information from the literature (1)
S-TSH	A03FA01	Metochlopramide	A7A3114B	Serum, Increase, Physiological: Following 10 mg orally marked increase within 1 h in euthyroid subjects: effect most marked in patients with primary hypothyroidism. Increased in euthyroidism and primary hypothyroidism; maximum effect 3 to 6 h after administration.
S-TSH	C02CA01	Prazosin	A6A3144B	Serum, Increase, Physiological: In 19 hypertensives treated for 12 weeks caused change from 3.63 μU/ml to 4.83 μU/ml.
S-TSH	H02AB07	Prednisone	A7A3244B	Serum, Increase, Physiological: Increased about twice with 1-2 mg/kg/d for 2-4 weeks in 10 children. Basal value increased two-fold in children given 1-2mg/kg/h for 2-4 weeks but TSH response to TRH unchanged.
S-TSH	H02AB**	Corticosteroids	A2E3144B	Serum, Decrease, Physiological: Usual response in patients on steroids.
S-TSH	N02BA01	Aspirin	A2C3144B	Serum, Decrease, Physiological: Decreased release after administration.
S-Prolactin	N05AA01	Chlorpromazin	A7E3114B	Serum, Increase, Physiological: Marked increase in normals in 2 h. Significant increase within 5 minutes of ingestion of 50 mg orally and 3 to 27 times baseline at 2h. Functions as potent dopamine antagonist in the tuberoinfundibular system. Effect dose related. Marked increase in male and female psychiatric patients treated for up to 4 weeks. Normal response to intravenous TRH.

glucocorticoid. All glucocorticoids can be covered with one code, H02AB**, in which the asterisk (*) means any character.

DISCUSSION

In Turku University Central Hospital, we have a computerized system for saving and interpreting individual medication data of the patients. These data are in a structured format and are highly valuable as such and can be used to improve the quality of patient care in several ways (12). Furthermore, to help clinicians in their daily work, we aim at improving the quality of laboratory information by producing alarms and alerts on drug effects on laboratory tests. For that purpose we need to build a wide rule base.

When building the rule base for drug-laboratory interferences, one has to be most critical in order to avoid the inconvenience of too many alerts in the final decision support system. The drug-laboratory interferences included in the rule base have to be classified and coded accordingly. This is the only possibility of defining an objective "cut-off level" for the interferences allowed to cause an alarm or an alert. Apart from this, the classification and coding of the interferences take into account the different requirements of each hospital and enable the users to select the interferences they want to be aware of.

Defining the "cut-off level" is difficult without knowledge of the final incidence of drug-laboratory interferences in the hospital patient population. If each laboratory test would have the same incidence of interfering drug effects, the total amount of alerts would increase enormously, which would be inconvenient for clinicians. As we have enough data in our medication database, we have the possibility of performing studies of the incidence of different alerts in a real hospital patient population. Only after performing these studies are we able to define the reasonable "cut-off level" of each parameter in the classification to make the system as useful as possible.

This year we have started a multi-center project called CANDELA (Computer Assisted Notification of Drug Effects on Laboratory tests) to collect data about drug effects on laboratory tests from many European centers. We are aiming at collecting

data in standardized format exploiting the coding described in this paper. This will enable us to obtain the data in a more standardized format than using free text. When the effect is analytical we will register the analytical method as well. We have made World Wide Web pages in the internet to describe the CANDELA-project (**http://www.utu.fi/~jarifors/candela.html**), and the DLI code (**http://www.utu.fi/~jarifors/dlicode.html**) . A page including a list of coded effects will be updated weekly as well (**http://www.utu.fi/~jarifors/dlidata.txt**).

A further advantage in this coding scheme is that it allows us to include preliminary information about the drug effects on laboratory tests which may be studied in prospective trials later. Here we can code the level of documentation as level 'D' (The interference is detected in incomplete case reports or is not yet documented) at first. Later, when more knowledge of the effect accumulates, the code for that effect will be changed. By doing this we are always aware of several suspected effects which should be tested in controlled clinical trials. This list of "need to know" influences will be made available for researchers using Internet. Thus, all laboratories carrying out controlled clinical trials on drugs have an opportunity to contribute to the development of this database.

CONCLUSIONS

When building automatic alarming systems, it is essential to minimize the amount of different expressions describing the data. In our opinion, a coding scheme is the most useful approach for this purpose. With a code it is possible to standardize the data available about drug effects on laboratory tests. Even if the code is quite rough, it helps to produce a very advanced and flexible system for automatic and cost-effective decision support for clinicians.

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